UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/446,601	04/03/2000	BERNARD ABRAMOVICI	IVD994	2604

27546 7590 06/04/2002

SANOFI-SYNTHELABO INC.
9 GREAT VALLEY PARKWAY
P.O. BOX 3026
MALVERN, PA 19355

EXAMINER
JAGOE, DONNA A

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 06/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/446,601	Applicant(s) ABRAMOVICI ET AL.	
	Examiner Donna A. Jagoe	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-22 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claims 1-22 are pending in this application.

Response to Arguments

Applicant's arguments filed March 25, 2002 have been fully considered but they are not persuasive. The rejection made in paper number 8 under 35 U.S.C. §103 is maintained and is hereby repeated. It is the applicant's position that the cited references would not have suggested the applicants' invention because if the invention would have been obvious, the absorption problem related to amiodarone would have been solved long ago. In response, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Since the disclosure provided by the PDR recognizes the problem of solubility in amiodarone, the Story reference provides motivation for one to solubilize insoluble drugs using non-ionic hydrophilic surfactants, and Margin-Algarra et al solve the absorption problem of amiodarone specifically by using the non-ionic hydrophilic surfactant, polysorbate 80, a *prima facie* case of obviousness is established.

While the examiner is in agreement with the arguments regarding the Story et al. reference where the applicant recites that "there is nothing in Story et al. that would

have suggested using such a small amount of non-ionic hydrophilic surfactant to both increase rate and reduce variability of absorption of either NSAIDS or amiodarone and dronedarone". Clearly, Martin-Algarra et al. recognize the problem that amiodarone has regarding erratic and variable absorption and also recites that a small amount of non-ionic hydrophilic surfactant solves the problem. Martin-Algarra et al. teach the absorption rate constants of amiodarone *decreased* as the surfactant concentration *increased* and absorption was unusually fast at *lower surfactant concentrations* (see abstract). Applicant alleges that the Martin-Algarra reference does not disclose oral administration or oral formulations. In response, Martin-Algarra et al. conclude that the convenience of designing a more reliable dosage form of amiodarone, containing a suitable dose of surfactant as a **solid** dispersion are entirely confirmed with polysorbate preparations being preferable (page 6, column 2). Applicant asserts that the weight percent of Martin-Algarra is from 666% to 140,000%. Page 5 of the reference in column 1 teaches 0.75 mg dissolved in 10 ml, which would be 7.5% by weight of the active principle in base form.

The Double Patenting rejection made in paper number 8 is maintained and is hereby repeated. Applicant asserts that the composition of the '778 patent is drawn to parenteral administration. While the composition of the '778 patent is drawn to parenteral formulations, the claims of the instant application are drawn to oral formulations in a gelatin capsule. It is known that liquid formulations may be placed in a gelatin capsule and administered orally. Regarding the buffer solution, the claim

language *comprising* leaves the claim open for the inclusion of unspecified ingredients, even in major amounts and as such, does not exclude the addition of a buffer solution.

(New) Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-6, 8-10, 13-15 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Martin-Algarra et al. (U).

The claims are drawn to a pharmaceutical composition comprising amiodarone hydrochloride in an oral formulation, such as a tablet and gelatin capsule, with the nonionic hydrophilic surfactant, polysorbate 80. Concentrations of from 1% to 50% by weight or 1% to 20% or 5% to 15% by weight of the active principle in base form are claimed.

Martin-Algarra et al. teach oral administration of amiodarone with polysorbate 90, teaching that the absorption rate constants of amiodarone decreased as the surfactant concentration increased, and absorption was unusually fast at lower surfactant concentrations. The concentration appears to be 0.75 mg dissolved in 10 ml, which would be 7.5%, by weight of the active principle in base form (page 5, column 1). A solid dispersion is recited (page 6, column 2, 4th full paragraph).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 7, 11, 12, 16 and 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martin-Algarra et al. (U).

The claims are drawn to a pharmaceutical composition comprising a benzofuran derivative such as amiodarone and dronedarone in a non-ionic hydrophilic carrier such as poloxamer 407 in amounts of from 200 to 400 mg in a capsule or tablet.

Martin-Algarra et al. teach amiodarone, a benzofuran derivative, in a non-ionic hydrophilic carrier such as polysorbate 80.

1. It does not teach the benzofuran derivative dronedarone;

2. it does not teach the non-ionic hydrophilic carrier, poloxamer 407 and;

3. it does not teach specific amounts such as 200 to 400 mg in a capsule or tablet.

1. It is prima facie obvious to substitute equivalents, motivated by the reasonable expectation that the respective species will behave in a comparable manner or give comparable results in comparable circumstances. *In re Ruff* 118 USPQ 343; *In re Jezel* 158 USPQ 99; the express suggestion to substitute one equivalent for another need not be present to render the substitution obvious. *In re Font*, 213 USPQ 532. It would have been obvious to substitute dronedarone for the amiodarone in Martin-Algarra since both amiodarone and dronedarone are both benzofuran derivatives it is expected that they would behave in a similar manner when placed on the non-ionic hydrophilic carrier, i.e. absorption would be enhanced when given by the oral route.

2. It is prima facie obvious to substitute equivalents, motivated by the reasonable expectation that the respective species will behave in a comparable manner or give comparable results in comparable circumstances. *In re Ruff* 118 USPQ 343; *In re Jezel* 158 USPQ 99; the express suggestion to substitute one equivalent for another need not be present to render the substitution obvious. *In re Font*, 213 USPQ 532. It would have been obvious to substitute the non-ionic hydrophilic surfactant poloxamer 407 for the non-ionic hydrophilic surfactant polysorbate 80 described in Martin-Algarra. Since they are both non-ionic hydrophilic surfactant they would be expected to behave in a similar manner.

3. As anyone of ordinary skill in the art will appreciate, preferred dosages are merely exemplary and serve as useful guideposts for the physician. The specific safe and effective amount will be vary, with such factors as the particular condition being

treated, the physical condition of the patient, the duration of treatment, the nature of the concurrent therapy (if any), the specific dosage form to be used, the carrier employed, the solubility of the formula therein and the dosage regimen desired for the composition. For these reasons it would have been obvious to use 50 to 500 mg of the active principal in the pharmaceutical composition.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna A. Jagoe whose telephone number is (703) 306-5826. The examiner can normally be reached on 6:30 A.M. - 3 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (703) 308-4725. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3230 for regular communications and (703) 308-7921 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0193.

dj
May 31, 2002

PRIMARY EXAMINER
GROUP 1600